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TECHNICAL NOTE

Certification of Water Content in NMIJ CRM 4222-a, Water Standard Solution 0.1 mg g⁻¹, by Coulometric and Volumetric Karl Fischer Titration

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The precise determination of water content is a very important issue and in high demand in many fields. To ensure precise and reliable measurements, certified reference materials (CRM) of water standards, whose concentrations are traceable to the International System of Units (SI), are required. The National Metrology Institute of Japan (NMIJ) has issued a CRM of water in mesitylene (0.1 mg g⁻¹) (NMIJ CRM 4222-a), with a very small uncertainty, for use in controlling the quality of analyses of trace water contents and confirming the validity of Karl Fischer (KF) titrators. This CRM is homogeneous, stable and low-hygroscopic under normal laboratory conditions; therefore, complex sample handling is not required. Characterization of the CRM was performed by coulometric and volumetric KF titrations. The certified value of the CRM (mass fraction of water) is 0.134 mg g⁻¹, and its expanded uncertainty is 0.004 mg g⁻¹ with a coverage factor 2, and is metrologically traceable to SI. We describe the measurement procedures and assays of trace water contents with linkage to SI and the technical details of the characterization of water in NMIJ CRM 4222-a. The developed CRM is particularly suitable for the quality control and validation of coulometric KF instruments and will be valuable in analyzing trace water contents.

1 Introduction

In many areas such as the pharmaceutical, chemical and food industries, water content must be controlled to appropriate levels from a quality control perspective and its precise determination is in high demand. Karl Fischer (KF) titration enables the simple and rapid measurement of water content and is widely used because of its several practical advantages compared with other methods for determining water, i.e., high accuracy, selectivity for water, wide measurable range and small sample quantity requirement.¹⁻¹¹ Because of these advantages, the KF titration has been adopted and used as a standard method in many cases.^{10,11}

However, it is generally challenging to measure trace amounts of water, because water is ubiquitously present under an atmospheric conditions. To accurately measure trace levels of water in organic and inorganic chemicals, the calibration of KF instruments and compensation for instrumental bias are

essential. Therefore, homogeneous and stable certified reference materials (CRM) for water content traceable to the International System of Units (SI) are required for the calibration and validation of the KF titration.

NIST SRM 2890 (water saturated 1-octanol) is well-known as a primary standard for water; however, its water content is quite high at (47.3 ± 1.0) mg g⁻¹.^{12,13} Thus, it is not appropriate for confirming the validity of coulometric KF instruments used for the analysis of trace water contents. In addition, its uncertainty is relatively high by considering its high water content. Furthermore, low-concentration (0.1 mg g⁻¹) water standards on the market are not always traceable to SI and the uncertainties in the guaranteed values for the water content are relatively large (5 % to 10 %). In these standard solutions, 1-octanol or xylene is used as the matrix solvent. Particularly in the former, the water content increases quickly under an ambient air condition because of the absorption of moisture since the solvent is highly hygroscopic. Therefore, such standard solutions are very difficult for users to handle. Recently, Wang et al. have reported the production of CRMs based on mixed organic solvents of 1-butanol, xylene and propylene carbonate¹⁴; however, their uncertainties are quite large (ca. 8.6 % at 0.1 mg g⁻¹ water standard).

Therefore, with these points in mind, the National Metrology Institute of Japan, National Institute of Advanced Industrial Science and Technology (NMIJ, AIST) has issued a

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new CRM (NMIJ CRM 4222-a) with a low water content and considerably low uncertainty. This CRM was certified by coulometric and volumetric KF titrations and the certified value is traceable to SI. We report here the technical details of the characterization of water for this CRM.

2 Materials and methods

2.1. Reagents and chemicals

Mesitylene, acetone, Aqualyte GRO-A and Aqualyte CN were purchased from Kanto Chemical (Tokyo, Japan). HYDRANAL-Composite 1 and HYDRANAL-Methanol Dry were obtained from Sigma-Aldrich Japan (Tokyo, Japan). NMIJ CRM 8301-a (bioethanol)^{15,16} was used for the titre determination of KF reagent.

2.2 Preparation of the candidate reference material

Immediately after opening 4 L of mesitylene was transferred into a 5-L glass bottle. The solution was stirred under ambient air for 3 h (24 °C, 20 % RH). The glass bottle was then screw-capped. To intercept from humidity change in the ambient air, two 5-L polyvinylidene difluoride (PVDF) bags containing laboratory air were attached to the bottle. After additional stirring for ca. 1 h, 8.5 mL of the solution was dispensed and sealed in a 10-mL amber glass ampoule without replacement of the headspace in the ampoules with inert gas. As the volume liquid in the reservoir decrease, air in headspace was filled from the PVDF bags. Two hundred and five ampoules were produced and preserved at room temperature (ca. 25 °C) until analysis.

2.3. Coulometric KF titration

The coulometric KF titration was performed using an AQ-2200 (Hiranuma Sangyo, Mito, Japan) instrument with a diaphragm cell. Aqualyte GRO-A and Aqualyte CN were used as the generator electrolyte and counter electrolyte, respectively. The interval time for the detection endpoint was 20 s and the minimum count was set to 1.0 µg. The current was set to the 'Slow' mode and automatic background correction was set to 'On'.

Sample handling and KF titration were performed under standard laboratory conditions of 24 °C to 26 °C room temperature and 20 % to 50 % relative humidity (RH). A 10-mL gas-tight sample lock syringe (Shimadzu GLC, Tokyo, Japan) was used to prevent sample evaporation and moisture absorption or desorption after sampling. After opening an ampoule, a VR-P rubber cap (Nichiden-rika Glass, Kobe, Japan) was attached immediately. Another hypodermic needle was inserted into the cap to avoid depressurizing the ampoule while sampling. The syringe was rinsed with ca. 1 mL of the sample solution and 6.5 mL (ca. 4.5 g) of the sample solution was carefully taken by syringe through the cap to avoid the formation of air bubbles. The syringe was weighed using a precision balance (AX205DR; Mettler Toledo, Greifensee, Switzerland) calibrated by the Japan Calibration Service System (JCSS). Then, 1.5 mL (ca. 1.3 g) of the aliquot was injected into the KF electrolytic cell. The syringe was weighed again to determine the net sample amount injected into the cell. After the measurement, an additional 1.5 mL of the aliquot was injected into the cell and measured triplicate for each ampoule. By using a rubber cap and gas-tight sample lock syringe,

moisture absorption was nearly eliminated at 24 °C to 26 °C and 20 % to 50 % RH.

The water content obtained by the coulometric KF titration was calculated as follows:

$$C_c = \frac{W_{\text{sample}} - W_{\text{blank}}}{M_{\text{sample}}} \quad (1)$$

where C_c is the water content obtained by the coulometric KF titration (mg g^{-1}), W_{sample} is the amount of water detected in the sample (mg), W_{blank} is the amount of water detected in the blank test (mg) and M_{sample} is the mass of the injected sample (g).

2.4. Confirmation of the traceability of the applied current in the coulometric KF titration

A 6581 Digital Multimeter (ADC, Tokyo, Japan), 2792A Standard Resistor (Yokogawa Electric, Tokyo, Japan), and TC110 Universal Counter (Yokogawa Electric), calibrated by the JCSS, were used for confirmation of the traceability of the electric charge applied in the coulometric KF titration.

2.5. Volumetric KF titration

The volumetric KF titration was performed using an MKS-500 (Kyoto Electric Manufacturing, Kyoto, Japan) instrument. HYDRANAL-Composite 1 was used as the titrating agent and HYDRANAL-Methanol Dry was used as the working medium. The interval time for the detection endpoint was 30 s. The detector mode was set to 'Normal' and titration speed was to 3. The stirring time before titration and the time for titration control were set to 0 s. Drift titration was set to 'Off' and the maximum titration volume was 10 mL. The titre determination of the KF reagent was performed using NMIJ CRM 8301-a (water content: $1.688 \pm 0.028 \text{ mg g}^{-1}$).^{15,16} The CRM was placed in the gas-tight sample lock syringe, weighed following the same procedure as for coulometric KF titration, and 2 mL (ca. 1.7 g) of the aliquot was injected into the KF cell.

The titre of the KF reagent was calculated as follows:

$$F = \frac{C_F \times M_F}{V_F - V_{F,\text{blank}}} \quad (2)$$

where F is the titre of the KF reagent (mg mL^{-1}), C_F is the water content in NMIJ CRM 8301-a (mg g^{-1}), M_F is the mass of NMIJ CRM 8301-a used for the titre determination (g), V_F is the amount of the KF reagent consumed for the titre determination (mL) and $V_{F,\text{blank}}$ is the amount of the KF reagent consumed in the blank test (mL).

To analyze the water content of the mesitylene sample solution, a 7-mL (ca. 6.1 g) aliquot was injected into the cell. The other conditions were the same as for the coulometric KF titration, except that the injection volume was 7 mL and each ampoule was analyzed once. The water content obtained by the volumetric KF titration was calculated as follows:

$$C_v = \frac{F \times (V_{\text{sample}} - V_{\text{blank}})}{M_{\text{sample}}} \quad (3)$$

where C_v is the water content obtained by the volumetric KF titration (mg g^{-1}), V_{sample} is the amount of the KF reagent consumed in the sample measurement (mL), V_{blank} is the amount of the KF reagent consumed in the blank test (mL) and M_{sample} is the mass of the injected sample (g).

2.6. Homogeneity assessment

The between-bottle homogeneity of the CRM was assessed by quantifying water in 3 subsamples taken from 10 ampoules,

selected through random sampling of the 205 subdivided ampoules. Quantification of water content was performed by coulometric KF titration. Analysis of variance (ANOVA) was used to analyze the concentration differences between bottles.¹⁷

2.7. Stability assessment

The long-term stability of the CRM was assessed by quantifying water content using the coulometric KF titration at 0.5, 1, 2, 3, 4, 6, 8 and 10 months after the homogeneity assessment (0 month).¹⁷

2.8. Measurement of density

The density of the CRM at room temperature was measured using an oscillational density meter (DMA 5000EX; Anton Paar GmbH, Graz, Austria). The density meter was calibrated using ultra-pure water (Anton Paar GmbH) at 20 °C ($0.99820 \pm 0.00011 \text{ g cm}^{-3}$). The measurements were conducted at 15 °C, 20 °C and 25 °C (triplicate per temperature). After the measurement, the line was rinsed and dried with acetone. About 3 mL of the sample was used for each analysis and the sample was reused at each temperature.

3 Results and discussion

3.1. Preparation of the candidate reference material

One of the defects of the existing water standards is the possibility of a change in water content after opening. For reliability of the CRM and the convenience of the CRM users, change of water content by moisture absorption or desorption have to be avoided. To reduce water content change during measurement and dispensation in ampoules, candidate reference materials were stirred under an ambient air to reach equilibrium between liquid and air. Among the various organic solvents, including alcohols, ethers, aliphatic and aromatic hydrocarbons, aromatic hydrocarbons were considered to be appropriate as a raw material for this CRM. Three kinds of candidate reference materials, mesitylene (water content after achieving equilibrium: ca. 0.13 mg g^{-1}), a mixture of mesitylene and 2,2,4-trimethylpentane (ca. 0.10 mg g^{-1}), and ethylbenzene (ca. 0.20 mg g^{-1}) were prepared, dispensed, and sealed under a humidity equal to the equilibrated humidity of their headspace. An inactive gas such as argon was not enclosed in the headspace, because it caused a ca. 0.02 mg g^{-1} decrease in the water content.

Finally, mesitylene was selected because its solubility in most of KF reagents is high; moreover it can be successfully analyzed and is not poisonous or deleterious. By adding aliphatic hydrocarbons such as hexane or 2,2,4-trimethylpentane, equilibrated water content decreased to 0.10 mg g^{-1} without regard to humidity; however, its solubility in the KF reagents decreased. Moreover, the long-term stability assessment indicates that the water content increases substantially in ethylbenzene during storage. Thus, mesitylene was selected as the matrix of the CRM.

3.2. Homogeneity assessment

Figure 1 shows the results of the homogeneity assessment (water contents relative to the mean of all analytical data). An ANOVA was used to analyze the concentration variation

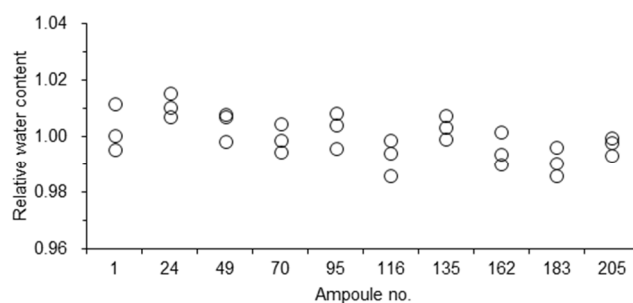


Fig. 1 Relative water contents in the homogeneity assessment.

between the bottles, and the mean squares within the groups (MS_{within}) and among the groups (MS_{among}) were calculated in accordance with ISO Guide 35.^{17,18} The inhomogeneity of the analyte, as evaluated by ANOVA, is reflected in the uncertainty of the certified value. Based on the results of the ANOVA, between-bottle variation was slightly significant ($p < 0.05$). However, the variance was small compared with the measurement uncertainty, as discussed in the following sections. Therefore, between-bottle inhomogeneity is not considered a concern for the raw material of this CRM.

The between-bottle standard deviation (s_{bb}) was calculated as follows:

$$s_{\text{bb}} = \sqrt{\frac{MS_{\text{among}} - MS_{\text{within}}}{n}} \quad (4)$$

If the repeatability of the measurement method was insufficient, the influence of analytical variation on the standard deviation between units (u_{bb}) was calculated and used to estimate the inhomogeneity. The value of u_{bb} was calculated as follows:

$$u_{\text{bb}} = \sqrt{\frac{MS_{\text{within}}}{n}} \sqrt{\frac{2}{v_{MS_{\text{within}}}}} \quad (5)$$

where $v_{MS_{\text{within}}}$ represents the number of degrees of freedom of MS_{within} . The calculated results for s_{bb} and u_{bb} were 0.519 % and 0.183 %, respectively. Because the value of s_{bb} was higher than that of u_{bb} , s_{bb} was adopted as the standard uncertainty associated with sample inhomogeneity.

3.3. Stability assessment

Stability assessment of the CRM is particularly important because atmospheric air rather than inert gas is enclosed in the headspace. If an oxidation reaction occurs in the ampoules during storage, the water content will be affected and will increase significantly. As noted above, the use of ethylbenzene instead of mesitylene as the solvent of water standard resulted in the water content increasing substantially during storage ($\geq 15 \%$ within 12 months). Accordingly, the assessment was carried out for 10-months with a frequency of analysis of at least once per 2 months.

Figure 2 shows the obtained water contents for the CRM (relative to the mean of the data at 0 month) stored at room temperature (ca. 25 °C). At each time point, two ampoules were analyzed. The slope of regression line b_1 was calculated in accordance with ISO Guide 35^{17,18} (Fig. 2):

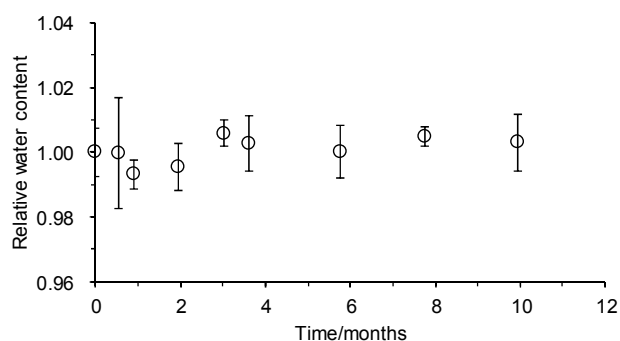


Fig. 2 Trend in the relative water content during long-term stability assessment. Circles and error bars represent the mean values and standard deviations, respectively.

$$b_1 = \frac{\sum_{i=1}^n (X_i - \bar{X})(Y_i - \bar{Y})}{\sum_{i=1}^n (X_i - \bar{X})^2} \quad (6)$$

where X_i and Y_i represent the elapsed time (days) and the concentration at i days relative to that at 0 day, respectively. The standard deviation of b_1 [$s(b_1)$] was calculated as follows:

$$s(b_1) = \frac{s}{\sqrt{\sum_{i=1}^n (X_i - \bar{X})^2}} \quad (7)$$

The values of s and the linear intercept b_0 were calculated as follows:

$$s^2 = \frac{\sum_{i=1}^n (Y_i - b_0 - b_1 X_i)^2}{n-2} \quad (8)$$

$$b_0 = \bar{Y} - b_1 \bar{X} \quad (9)$$

The significance of the instability was tested as follows:

$$|b_1| < t_{0.95, n-2} \times s(b_1) \quad (10)$$

where $t_{0.95, n-2} = 2.36$ (with two degrees of freedom at level of confidence $p = 0.95$) and $|b_1|$ and $s(b_1)$ were calculated using Eqs. 6 and 7, respectively. The slope of the line showed no significant difference, as the requirement of Eq. 10 was satisfied.

The uncertainty due to long-term instability (u_{its}) is $t \times s(b_1)$, where t represents the expiry date (days). The expiry date of this CRM has been determined to be 2 years, and t is 896 days (from the date that the characteristic value was determined to the expiry date). Based on the results of the stability assessment, $s(b_1)$ was determined to be 1.25×10^{-5} . Therefore, u_{its} was calculated as 1.12 %.

3.4. Confirmation of the traceability of the applied current in coulometric KF titration

To confirm the traceability of the applied current in the coulometric KF titration used in this study, the standard resistor was connected in series in the circuit of the applied current on the KF instrument and the voltage drop at both ends was measured by the voltmeter. The applied current was calculated according to the Ohm's law with resistance and voltage values and the time was measured using a universal frequency counter. The values of water contents in NMIJ CRM 8301-a obtained using the JCSS-calibrated titrator and KF instrument were not

different significantly. The uncertainties of the standard resistor and other components were negligible; thus, in this study, the values for the water content obtained using the KF instrument were used directly without correction.

In analyzing this CRM, an accurate determination of 100 μg to 200 μg water was required. To confirm the efficiency of electrolysis in the range of these concentration, using NMIJ CRM 8301-a as a sample solution, the injection volumes were adjusted. The correlation between the water content detected by the KF instrument and the calculated water content was then evaluated (Fig. 3). Good linearity with a slope 1 and correlation coefficient were obtained ($y = 0.9998x + 0.2874$, $r^2 = 0.9999$).

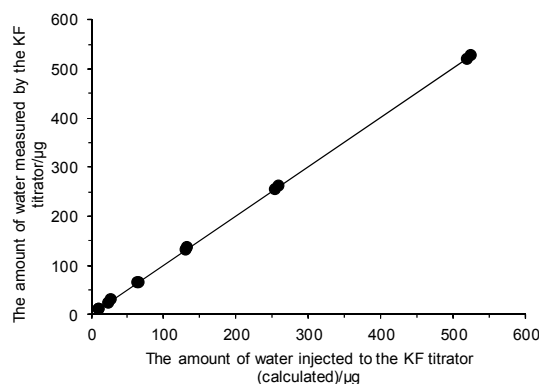


Fig. 3 Correlation of the amount of water measured and calculated in analyzing NMIJ CRM 8301-a by coulometric KF titrator used in this study.

Furthermore, another coulometric KF titrator (MKC-510N; Kyoto Electronic Manufacturing) was used for the analysis of this CRM and the obtained water content was $(0.1331 \pm 0.0005) \text{ mg g}^{-1}$ (mean \pm SD; $n = 3$); thus, the difference between the instruments was not significant.

For the volumetric KF titration, traceability depends on the reference materials for which water content is known and used for titre determination of the KF reagents. In this study, because NMIJ CRM 8301-a was used as the reference material, traceability to SI was ensured.

For these reasons, in this study, the coulometric and volumetric KF titrations were performed to assay water with traceability to SI.

3.5. Analytical results, certified value, and uncertainty in the certified value

Table 1 lists the water contents determined using the coulometric and volumetric KF titrations of five and ten randomly selected ampoules, respectively. The water contents determined by both the methods were in good agreement.

The certified value is the weighted mean of the analytical results obtained by both the methods, where $1/u_i$ (u_i : uncertainty in the result obtained by each method) was used as the weight. The weighted mean and the relative combined uncertainty are shown in Table 2.

The uncertainty due to the analytical method (u_{anal}) was calculated using the uncertainties of the quantitative values and weights. Thus, u_{anal} was determined to be 0.277 %. The uncertainty of the method (u_{method}) is regarded as the between-group variance obtained by ANOVA from the results (between the means for each ampoule), and determined to be 0.289 %.

Table 1 Water contents obtained by coulometric and volumetric KF titration.

Coulometric KF titration					
Ampoule no.	25	52	103	154	201
Water content (mg g ⁻¹)	0.1339	0.1333	0.1336	0.1311	0.1338
	0.1330	0.1332	0.1333	0.1341	0.1312
	0.1349	0.1352	0.1346	0.1346	0.1335
Mean	0.1340	0.1339	0.1338	0.1333	0.1328
Total mean	0.1336				
Volumetric KF titration					
Ampoule no.	19	28	67	84	107
Water content (mg g ⁻¹)	0.1352	0.1339	0.1372	0.1352	0.1349
Ampoule no.	115	129	147	174	202
Water content (mg g ⁻¹)	0.1349	0.1359	0.1363	0.1307	0.1322
Total mean	0.1346				

Table 2 Weighted mean and relative combined uncertainty.

	Quantitative value (mg g ⁻¹)	Uncertainty (mg g ⁻¹)	Uncertainty (relative value)
Coulometric KF titration	0.1336	0.000317	0.00237
Volumetric KF titration	0.1346	0.00153	0.0113
Weighted mean	0.1337	0.000371	0.00277

The uncertainty in the certified value (u_{CRM}) was evaluated by combining u_{anal} , u_{method} , u_{hom} and u_{IIS} . The values used for u_{hom} and u_{IIS} were obtained from the homogeneity and stability assessments, respectively.

Finally, Table 3 summarizes the uncertainty budget for the certified value. The certified value of water was 0.134 mg g⁻¹ and the expanded uncertainty (coverage factor, $k = 2$) was 0.004 mg g⁻¹.¹⁹

Table 3 Uncertainty budget.

Uncertainty source	Unit	Value	Uncertainty
Certified value	C_{water}	mg g ⁻¹	0.1337
Analytical method	u_{anal}	(relative value)	0.00277
Between method	u_{method}	(relative value)	0.00289
Inhomogeneity	u_{hom}	(relative value)	0.00519
Instability	u_{IIS}	(relative value)	0.0112
Combined uncertainty	u_{CRM}	(relative value)	0.0130
	u_{CRM}	mg g ⁻¹	0.000174

3.6. Information for users

When this CRM was taken and its water content was measured at 16 % RH (23 °C) and at 67 % RH (26 °C), significant change of water content was not observed within 15 minutes and the obtained results remained in the uncertainty of the certified value. For the measurements, just after breaking the ampoule, the rubber cap was attached on the ampoule. The sample was taken from the bottom of the ampoule using a gas-tight syringe through the cap.

3.7. Density of the CRM

The measured values for the density of this CRM using an oscillational density meter were 0.86111 g cm⁻³ at 25 °C, 0.86520 g cm⁻³ at 20 °C, and 0.86927 g cm⁻³ at 15 °C. Therefore,

the water content of this CRM was estimated as (0.115 ± 0.003) mg cm⁻³ at 25 °C.

4. Conclusions

A homogeneous, stable and low-hygroscopic CRM consisting of mesitylene for the determination of 0.1 mg g⁻¹ water content was produced and certified. Coulometric and volumetric KF titrations were performed to accurately determine the water content with traceability to SI and with measurement uncertainties. The CRM was prepared, dispensed, and sealed under humidity equal to the equilibrated humidity of the headspace. In this way, the uncertainty due to the inhomogeneity between ampoules could be minimized. In addition, after ampoule was opened, the water content did not change significantly because of moisture absorption. Furthermore, uncertainty due to long-term instability of such water standards was evaluated in detail for the first time and the uncertainties due to these factors were all reflected in the uncertainty of the certified value. The relative uncertainty in the certified value was 2.6 % (expanded uncertainty with a coverage factor of 2), which is considerably low. The newly characterised CRM can be applied for the calibration or validation of measurement procedures to ensure precise and comparable results and will be valuable for analyzing trace water contents.

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